



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/GB96/00952 <b>(22) International Filing Date:</b> 19 April 1996 (19.04.96) <b>(30) Priority Data:</b> 9508023.0 20 April 1995 (20.04.95) GB <b>(71) Applicant (for all designated States except US):</b> SCOTIA HOLDINGS PLC [GB/GB]; Efamol House, Woodbridge Meadows, Guildford, Surrey GU1 1BA (GB). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> HORROBIN, David, Frederick [GB/GB]; Scotia Pharmaceuticals Limited, Scotia House, Castle Business Park, Stirling FK9 4TZ (GB). KNOWLES, Philip [GB/GB]; Scotia Pharmaceuticals Limited, Research & Development Centre, Kingstown Broadway, Kingstown Industrial Estate, Carlisle CA3 0HA (GB). MANKU, Mehar [GB/GB]; Scotia Pharmaceuticals Limited, Research & Development Limited, Kingstown Broadway, Kingstown Industrial Estate, Carlisle CA3 0HA (GB). BONNETT, Raymond [GB/GB]; Queen Mary & Westfield College, Chemistry Dept., Mile End Road, London E1 4NS (GB). STEWART, John, Charles, Marshall [GB/GB]; Scotia Pharmaceuticals Limited, Efamol House, Woodbridge Meadows, Guildford, Surrey SU1 1BA (GB).		<b>(74) Agents:</b> STURT, Clifford, Mark et al.; J. Miller & Co., 34 Bedford Row, Holborn, London WC1R 4JH (GB).  <b>(81) Designated States:</b> AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>

**(54) Title:** FATTY ACID DERIVATIVES**(57) Abstract**

An N-alkylpolyhydroxyamine salt of an n-6 or n-3 essential fatty acid (EFA) that is beyond the 6-desaturation step, or of any polyunsaturated fatty acid, other than those belonging to the n-6 and n-3 series, having 16 to 26 carbon atoms and up to six double bonds, the double bonds being in the cis or trans configuration, the salt being formed with the fatty acid either as such or in the form of a covalent derivative, through the carboxyl group, of a bifunctional compound itself having a free acid function.

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## Fatty Acid Derivatives

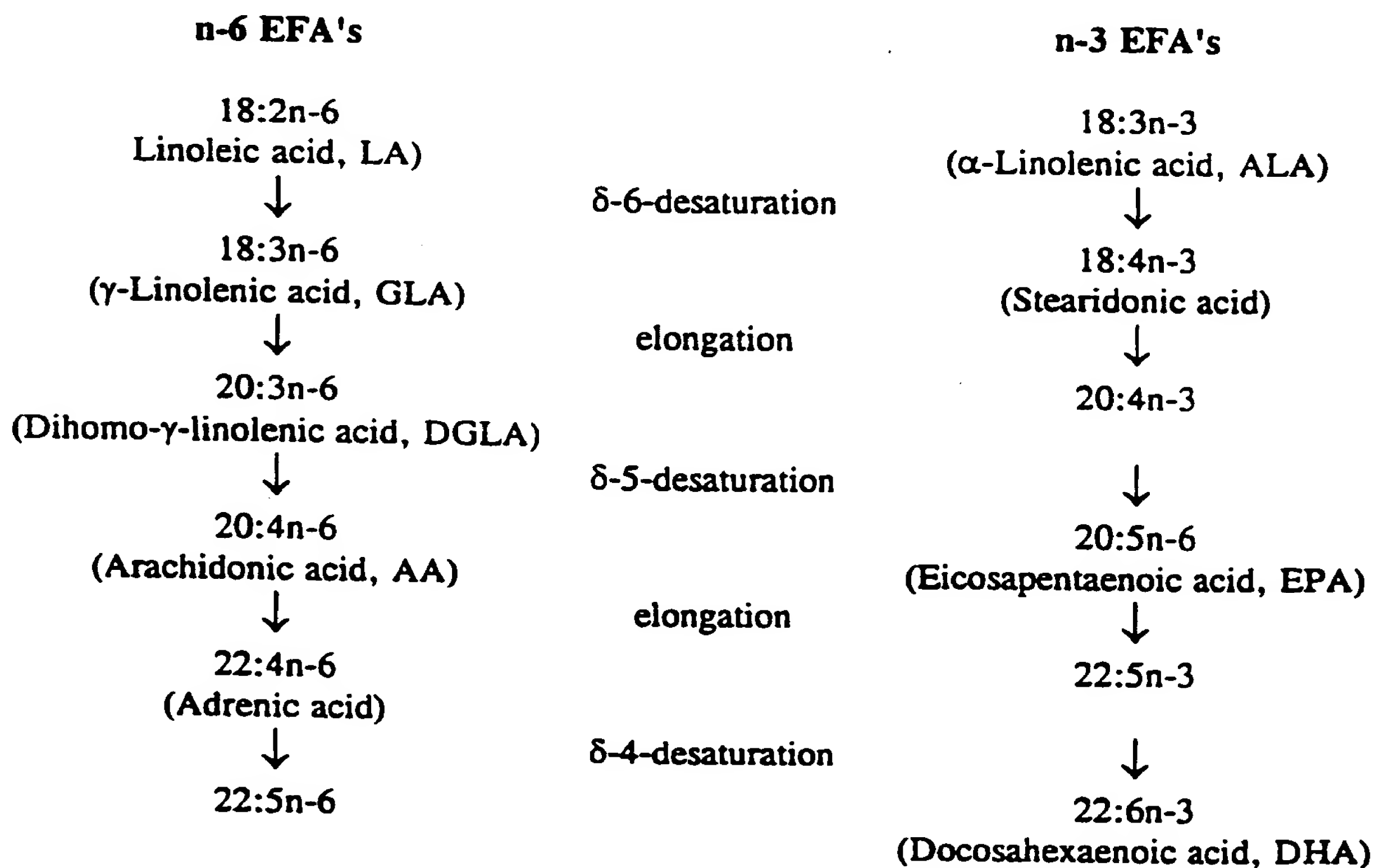
### Field of the Invention

The invention relates to fatty acid derivatives.

### Background

Numerous previous patent applications by the inventors have documented important therapeutic actions of the n-6 and n-3 essential fatty acids. These essential fatty acids (EFAs) and their bodily conversion pathways are set out in Table 1 below.

Table 1



The acids, which in nature are of the all-cis configuration, are systematically named as derivatives of the corresponding octadecanoic, eicosanoic or docosanoic acids,

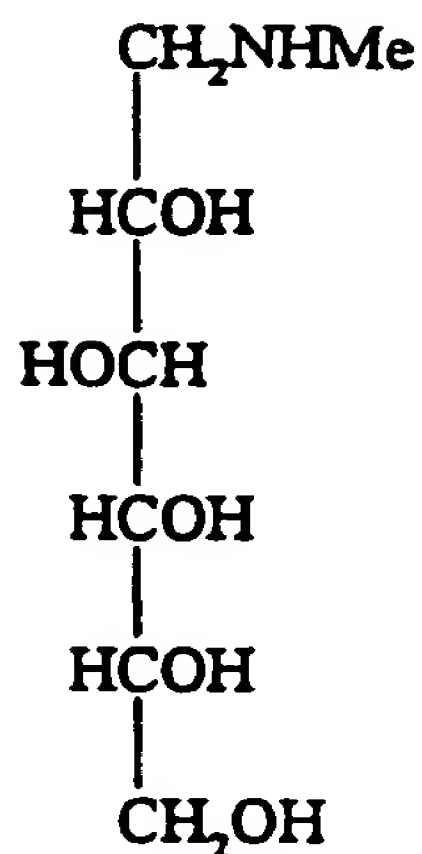
e.g. z,z octadeca-9,12-dienoic acid or z,z,z,z,z,z docosa- 4,7,10,13,16,19 -hexaenoic acid, but numerical designations based on the number of carbon atoms, the number of centres of unsaturation and the number of carbon atoms from the end of the chain to where the unsaturation begins, such as, correspondingly, 18:2n-6 or 22:6n-3, are convenient. Initials, e.g. EPA and shortened forms of the name e.g. eicosapentaenoic acid are used as trivial names in some of the cases.

The preferred fatty acids of the present invention are the ten n-6 and n-3 essential fatty acids that are beyond the 6-desaturation step, desirably in all -cis form, but the invention is not limited to them nor to acids in which the chain contains repeating -CH=CH-CH<sub>2</sub>- units. Columbinic acid and  $\alpha$ -parinaric acids, for example, are also suitable, being e,z,z -octadeca -5,9,12 -trienoic acid and z,e,e,z -octadeca -9,11,13,15 -tetraenoic acid, respectively.

The therapeutic actions include desirable effects in many different diseases including cardiovascular diseases, diabetes, skin diseases, inflammatory diseases and immunological diseases, cancer, psychiatric disorders, renal diseases, prostatic disorders and gastrointestinal and other diseases.

By their nature, EFAs are highly hydrophobic compounds which are soluble in water to a negligible extent. However, there are many reasons why it would be desirable to have a water soluble form of these compounds. Such water soluble derivatives may, for example be more easily absorbed from the gut via the hepatic portal system; may be given intravenously with ease; and may be used in many other ways such as in topical formulations, formulations for local administration, innovative oral formulations including drinks, enteral foods, and skin care preparations including lotions, shampoos, creams and so on.

Meglumine (N-methyl glucamine, an N-alkyl polyhydroxy amine) is an agent which is widely used in pharmaceutical formulations and which has an excellent safety profile. The formula is:



[C<sub>7</sub>H<sub>17</sub>N<sub>0</sub>O<sub>5</sub>; M.W. 195.2]

We have found that the meglumine derivatives of EFAs are highly water soluble and can therefore be used in many different ways in the formulation of pharmaceuticals, foods, nutritional supplements, skin care products and drinks of many different sorts. The invention can also be applied to a wide variety of other polyunsaturated fatty acids, other than those belonging to the n-6 and n-3 series, which have 16 to 26 carbon atoms, up to 6 double bonds, and with the double bonds in either the cis or trans configuration.

### The Invention

The invention provides water soluble N-alkylpolyhydroxyamine salts of polyunsaturated fatty acids as above, particularly the n-6 and n-3 essential fatty acids that are beyond the 6-desaturation step. These salts are stoichiometric and of the form (1) where A<sup>+</sup> is, in particular, protonated N-methyl glucamine (Meglumine), but also protonated glucamine or any other N-alkylpolyhydroxy amine, and FA<sup>-</sup> is the anion of the EFA or other fatty acid:-



The invention further relates to the formation of salts wherein the EFAs or other fatty acids are in the form of derivatives formed by covalent combination of the fatty acid, through the carboxy group and thus normally as an ester or amide, with a

bifunctional compound having also a free acidic function. Examples are ascorbic acid, where the fatty acid is as a 6-ester, and salicylic acid.

The salts may for example be presented as aqueous solutions or as lyophilised powders. The solutions may also be constituted in 0.9% sterile saline. Such solutions may be prepared by the slow addition, with good stirring and under nitrogen, of the requisite amount of the fatty acid or derivative to an aqueous or saline solution of the sugar amine until a clear solution is obtained (pH range : 5 to 9).

The solubilities of some of the lyophilised salts compared to starting EFAs in various solvents are given in Table 2 below, by way of illustration of their physico-chemical characteristics:-

**Table 2 - Solubilities (w/v) at 25°C with sonication**

Solvent	Meglumine Salts of EFAs	EFAs
Water	> 20% but < 40%	< 1%
Ethanol	> 20% but < 50%	Miscible in all proportions
Chloroform	> 20% but < 50%	Miscible in all proportions

In use the salts may be prepared for delivery by oral, parenteral, enteral or other routes. Doses of any one or more of the fatty acids may be 1 mg to 200 g, preferably 10 mg to 20 g and very preferably 50 mg to 2 g/day. When applied topically the concentration of the fatty acid may range from 0.0001 to 50% preferably 0.01 to 30% and very preferably 0.1 to 10% by weight of the preparation.

### **Examples of Preparation of Salts**

#### **Example 1 (Meglumine salt of DHA)**

N-Methyl glucamine B.P (595.5 mg, 3.05 mmol) is dissolved in pure water (8.0 ml) and, under nitrogen with efficient stirring, there is added, dropwise over 5 mins,

*z,z,z,z,z,z* - docosa - 4,7,10,13,16,19 - hexaenoic acid, DHA (1.0g). The mixture is stirred until a clear 20% w/v solution of *N-methyl glucammonium/z,z,z,z,z,z* - docosa - 4,7,10,13,16,19 - hexaenoate (Meglumine DHA) is formed. The solution is filtered through a 0.2  $\mu$ m filter and lyophilisation gives a white waxy powder readily reconstituted in water to a solution of up to 30% w/v.

**Example 2** (Meglumine salt of GLA)

By proceeding in a similar manner to Example 1 but replacing the DHA with an equivalent amount of *z,z,z* - octadeca - 6,9,12 - trienoic acid, GLA, there is formed *N-methyl glucammonium z,z,z* - octadeca - 6,9,12 - trienoate (Meglumine GLA) in a 20% w/v aqueous solution.

**Example 3** (Meglumine salt of DGLA)

By proceeding in a similar manner to Example 1 but replacing the DHA with an equivalent amount of *z,z,z* - eicosa - 8,11,14 - trienoic acid, DGLA, there is formed *N-methyl glucammonium z,z,z* - eicosa - 8,11,14 - trienoate.

**Example 4** (Meglumine salt of AA)

By proceeding in a similar manner to Example 1 but replacing the DHA with an equivalent amount of *z,z,z,z* - eicosa - 5,8,11,14 - tetraenoic acid, AA, there is formed *N-methyl glucammonium z,z,z,z* - eicosa - 5,8,11,14 - tetraenoate (Meglumine AA) in a 20% w/v aqueous solution.

**Example 5** (Meglumine salt of Ascorbyl GLA)

Hydrogen chloride gas (2.0 g) is bubbled into N,N-dimethyl acetamide (26.5 ml) at 0°C. To the resultant slurry is added a slurry of ascorbic acid (9.69 g) in dichloromethane (13.25 ml) and the mixture is stirred at 0°C until solution occurs. To this solution at 0°C under nitrogen, is added *z,z,z* - octadeca - 6,9,12 - trienoyl chloride (14.8 g) over a period of 4 hours and the resulting mixture is allowed to stand at the

above temperature for 18 hours and room temperature for 1 hour. On cooling to 0°C, ethyl acetate (200 ml) and water (100 ml) are added and the mixture stirred for 1 hour. The organic layer is washed with brine (5 x 100 ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated at 50°C/10 mm Hg then 50°C/0.1 mm/4 hours to give ascorbic acid 6-[(z,z,z)-octadeca-6,9,12-trienoate] (18.25 g, 88%) (ascorbyl GLA) as a pale yellow wax.

A soap-like emulsion of the ascorbyl GLA (112 parts) in pure water (600 parts) is formed by vigorous stirring for 10 - 15 mins under nitrogen. To this mixture is added with stirring N-methyl glucamine B.P. (66 parts) in pure water (200 parts) over a period of 10 - 15 mins until a clear solution is obtained. The mixture is filtered through a 0.2µm filter and then lyophilised to give N-methyl glucammonium 6 - (z,z,z - octadeca - 6,9,12 - trienoyl) ascorbate as a hygroscopic very pale yellow solid.

Example 6 (Meglumine salt of Salicylic Acid gamma linolenate)

By proceeding in a similar manner but replacing the ascorbyl GLA with an equivalent amount of 2 - (z,z,z - octadeca - 6,9,12 - trienoyloxy) benzoic acid, which is the GLA derivative of salicylic acid, there is formed N-methyl glucammonium 2 - (z,z,z - octadeca - 6,9,12 - trienoyloxy) benzoate. The GLA derivative of salicylic acid was itself prepared by the following method.

**Stage 1: 2,2,2-Trichloroethyl salicylate:-** A mixture of salicylic acid (90 g), 2,2,2 - trichloroethanol (270 g) and concentrated sulphuric acid (50 g) was stirred and heated at 100°C for 4 hours. The mixture was diluted with chloroform (800 ml) and extracted with water (2 x 500 ml). After further extraction with saturated aqueous sodium bicarbonate solution (1000 ml), the organic layer was washed with water (2 x 500 ml) and dried (Mg SO<sub>4</sub>). The chloroform and excess trichloroethanol were removed *in vacuo* (65°C/20 mm Hg) and the product was distilled (110-112°C/0.5 mm Hg) to give 2,2,2 - trichloroethyl salicylate (104 g, 59%) as a clear liquid which solidified on cooling.



**Stage 2: 2,2,2-Trichloroethyl 2-[(z,z,z) octadeca-6,9,12-trienoyloxy]**

**benzoate:-** To a solution of 2,2,2-trichloroethyl salicylate (104g) in dry pyridine (500 ml) at 0-5°C and under nitrogen was added (z,z,z) octadeca-6,9,12-trienoyl chloride (137.5g) dropwise over a period of one hour. The reaction mixture was allowed to stir for twenty hours at room temperature and then the pyridine was removed *in vacuo* (25°C/0.5mm Hg). The residue was dissolved in diethyl ether (2000 ml) and water (1000 ml) and the resulting two phase system was shaken and acidified slowly to pH1 by addition of 2M hydrochloric acid. The diethyl ether layer was separated and washed with water (4 x 1000 ml), adding sodium chloride to break any emulsion that formed. After drying the organic layer (Na<sub>2</sub>SO<sub>4</sub>), the solvent was removed *in vacuo* to give an orange/brown oil. This was subjected to MPLC (Column size: 15 cm dia. x 40 cm, Column packing: Matrex silica, pore size 60A, particle size 35-70µm, Solvent: initially hexane, then 15% diethyl ether in hexane, Fraction size: 1000 ml). The requisite fractions were evaporated *in vacuo* to give 2,2,2-trichloroethyl-2-[(z,z,z) octadeca-6,9,12-trienoyloxy] benzoate. (189g, 93% yield) as a pale yellow oil.

**Stage 3: 2-[(z,z,z) Octadeca-6,9,12-trienoyloxy] benzoic acid:-** 2,2,2-

Trichloroethyl-2-[(z,z,z) octadeca-6,9,12-trienoyloxy] benzoate (151g) was dissolved in a mixture of tetrahydrofuran (750 ml), acetic acid (675 ml) and water (75 ml). Zinc dust (150g) was added. The mixture was stirred at room temperature under nitrogen for 1.5 hours and then allowed to stand for twenty hours. Excess zinc and zinc salts were filtered off through Celite washing the filter pad with tetrahydrofuran (100 ml) and the filtrate was evaporated at 25°C/10mm Hg to remove the tetrahydrofuran. The acetic acid and water was then removed at 25°C/0.5mm Hg. Higher temperatures tend to decompose the product. The resulting oil was dissolved in diethyl ether (1000 ml) and the resulting solution was washed with water (4 x 200 ml). After drying (Na<sub>2</sub>SO<sub>4</sub>), the ether was evaporated (25°C/10mm Hg) to give a pale yellow oil which was subjected to a dry column (Packing: Matrex silica (1 Kg), pore size 60A, particle size 35-70µm, Fraction size: 1000 ml). The requisite fractions were collected, the solvent evaporated

as before, the last traces being removed at 25°C/0.1mm Hg to give 2-[(z,z,z) octadeca-6,9,12,-trienoyloxy] benzoic acid, (77.8g, 68%) as a pale orange oil which solidified to a wax in the refrigerator.

#### Use Examples

1. A sterile solution for topical or local administration containing 0.1 - 20% by weight of any one of the EFA derivatives of preparative Examples 1 to 4.
2. An oral pharmaceutical preparation containing 100 mg to 1 g in 5 ml of any one of the EFA derivatives of preparative Examples 1 to 6.
3. A sterile pharmaceutical solution for intravenous administration containing 0.1 to 20% by weight of any one of the EFA derivatives of preparative Examples 1 to 6.
4. A skin or hair care preparation containing a concentration of 0.1 to 40% by weight of any one of the EFA derivatives of preparative Examples 1 to 4.
5. A milk, fruit juice or other food or drink preparation containing a concentration of 0.1 to 40% by weight of any one of the EFA derivatives of preparative Examples 1 to 4 or 5.

### Claims

1. An N-alkylpolyhydroxyamine salt of an n-6 or n-3 essential fatty acid (EFA) that is beyond the 6-desaturation step, or of any polyunsaturated fatty acid, other than those belonging to the n-6 and n-3 series, having 16 to 26 carbon atoms and up to six double bonds, the double bonds being in the cis or trans configuration, the salt being formed with the fatty acid either as such or in the form of a covalent derivative, through the carboxyl group, of a bifunctional compound itself having a free acid function.
2. A salt according to claim 1 wherein the N-alkylpolyhydroxyamine is N-methylglucamine.
3. A salt according to claim 1 or 2 wherein the fatty acids are selected from gamma-linolenic acid, dihomogamma-linolenic acid, arachidonic acid, adrenic acid, the 22:5 n-6 acid, stearidonic acid, the 20:4 n-3 acid, eicosapentaenoic acid, the 22:5 n-3 acid, docosahexaenoic acid.
4. A salt according to claim 1 or 2 wherein the fatty acids are selected from columbinic acid and alpha-parinaric acid
5. A salt according to any preceding claim, wherein said bifunctional compound having a free acid function is ascorbic acid or salicylic acid.
6. Use of a salt according to any one of claims 1 to 5 in the preparation of oral, topical, enteral or parenteral pharmaceuticals.
7. Use of a salt according to any one of claims 1 to 5 in the preparation of nutritional supplements in tablet, capsule, solution, suspension, emulsion or other form.

8. Use of a salt according to any one of claims 1 to 5 in the preparation of products for skin or hair care.
9. Use of a salt according to any one of claims 1 to 5 in the preparation of foods and drinks, including fortified fruit, milk and fruit juice products.
10. A composition for pharmaceutical, nutritional or cosmetic use comprising a salt according to any one of claims 1 to 5 in association with a suitable diluent or carrier.

## INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/GB 96/00952

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07C57/03 C07C215/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB,A,431 130 (E.I.DU PONT DE NEMOURS) 28 March 1934 see page 1, line 49 - line 61 see page 1, line 79 - line 91 see page 2, line 5 - line 64 see claims 1,2 ---	1,8
X	US,A,2 703 798 (SCHWARTZ) 8 March 1955 see column 2, line 31 - line 47 see column 3; examples 2-4 see claims 1,3,6 ---	1
X	US,A,1 985 424 (PIGGOT) 25 December 1934 see column 1, line 38 - line 48 see column 2, line 16 - line 35 see claims 1,3,12,16 ---	1
	--- -/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

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- \*&\* document member of the same patent family

Date of the actual completion of the international search

27 June 1996

Date of mailing of the international search report

-5.07.96

Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/GB 96/00952

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO,A,92 06984 (THE PROCTER &amp; GAMBLE CO.)  30 April 1992  see page 13, line 15 - page 14, line 15  see page 17, line 23 - line 37  -----</p>	1

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB96/00952

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
The drafting of the claim 1 encompasses an enormous amount of products, the claim does not find support in the description. On grounds of Articles 6 and 17.2.a(ii) the PCT (conciseness of claims) and of the Guidelines for Examination in the EPO, Part 8, Chapter III, 2.2. (economic reasons) the search has been based on the preparation examples disclosed in the description. (Claims not searched: 4)
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a). (Claims searched incompletely: 1)

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 96/00952

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A-431130		NONE	
US-A-2703798	08-03-55	NONE	
US-A-1985424	25-12-34	NONE	
WO-A-9206984	30-04-92	AU-B- 660628	06-07-95
		AU-B- 8768291	20-05-92
		AU-B- 8907291	20-05-92
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		SK-A- 21793	07-07-93
		TR-A- 25865	01-09-93
		US-A- 5334764	02-08-94
		WO-A- 9206699	30-04-92